IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: James P. Elia	)	
	)	
SERIAL NO.: 09/836,750	)	EXAMINER: E.C. Kemmerer, Ph.D.
	)	
FILED: April 17, 2001	)	
	)	GROUP ART UNIT: 1646
FOR: METHOD FOR GROWING MUSCLE IN A HUMAN HEART	)	

SECOND SUPPLEMENTAL DECLARATION
OF RICHARD HEUSER, M.D., F.A.C.C., F.A.C.P.

I, Richard Heuser, declare as follows:

1. I have offices at 500 West Thomas Road, Suite 900, Phoenix, Arizona 85013.

2. This Second Supplemental Declaration is submitted in addition to my previous Declaration, dated June 5, 2003 and my Supplemental Declaration dated February 4, 2004. No changes are made to either of such previous Declarations.

3. My Curriculum Vitae (hereinafter "CV") is attached as Exhibit A to my Declaration of June 5, 2003.

4. It is my understanding that the Examiner in charge of the above-identified patent

application, in an Office Action dated June 1, 2004 for related patent application Serial No. 09/794,456, questioned my qualification, for the first time, to render my previous opinions mentioned in above Paragraph 2. It is my further understanding that the basis for such questioning was that the Examiner noted that I did not report experience with cellular therapy. I desire to provide the information contained in following paragraph 5 so that the Examiner can consider such information in this application, as well.

5. I am currently Director of Cardiovascular Research at St. Joseph's Hospital and Medicine Center, and I serve as Clinical Professor of Medicine at University of Arizona College of Medicine. Over the past six years, I have worked in gene therapy, as well as muscle regeneration for the treatment of cardiomyopathy.

In my CV, you will note reference to work that was done with Sulzer Medical involving a rabbit hind limb model to stimulate peripheral vascular disease. I injected a growth mixture that included FGF, etc. into the hind limb model.

In my U.S. Patent No. 6,190,379 entitled "Hot Tip Catheter," I developed a technique to deliver radiofrequency (PMR). In the full embodiment of the patent, I discuss delivery of protein and/or muscle cells in the myocardium using the inventive technique.

I have been involved as a member of the scientific advisory board with the world leader in cardiomyocyte regeneration, Bioheart, Miami Lakes, Florida. This company has been involved with laboratory and clinical trials using skeletal muscle cultured and modified. The sample is then delivered into the myocardium via a surgical or catheter approach.

6. I have read and understood the disclosures of the above-referenced patent application at page 20, line 10 through page 21, line 17; and page 44, line 19 through page 46, line 16. Such disclosures are the same as I read and understood in my previous Declaration and

Supplemental Declaration. A copy of such disclosures is attached hereto as Second Supplemental Declaration Exhibit A.

7. I note that the disclosures referenced in above Paragraph 6 relate to using a growth factor for promoting the growth of soft tissue and, more specifically, to a method which may use such growth factors for growing a new portion of a human heart by growing new cardiac muscle in the heart.

8. I have read and understood the claims set forth in Second Supplemental Declaration Exhibit B and have been informed that such claims are currently presented in this application.

9. Based upon above Paragraphs 6-8, it is my opinion that one skilled in the medical arts, armed with the knowledge in such paragraphs, would be enabled to practice the method set forth in Second Supplemental Declaration Exhibit B and to predictably anticipate the results defined therein without need for resorting to undue experimentation.

10. I believe that one skilled in the medical arts, upon reading the disclosures in above , such as multifactorial and non-specific cells,Paragraph 6, would understand that cellular growth factors are included in such disclosures. Moreover, such skilled person would understand the disclosure on page 45 to be authored as an illustration of various modes of delivery of growth factors, whether they are genes or other genetic material; and that such skilled person would further understand that the disclosures on pages 45 and 46 describe genetic material to include appropriate cells and genes.

11. Declarant states that the above opinion was reached independently.

Declarant understands that (1) any willful false statements and the like made herein are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon, and (2) that all statements made of Declarant's own knowledge are true and that all statements made on information and belief are believed to be true.

Further Declarant sayeth not.

Date: 4/18/04

Richard Heuser, M.D., F.A.C.C., F.A.C.P.

SECOND SUPPLEMENTAL DECLARATION
EXHIBIT A

DISCLOSURES
APPLICATION SERIAL NO. 09/836,750

PAGE 20, LINE 10 – PAGE 21, LINE 15

Growth factors can be utilized to induce the growth of "hard tissue" or bone and "soft tissues" like ectodermal and mesodermal tissues. As used herein, the term growth factor encompasses compositions and living organisms which promote the growth of hard tissue, such as bone, or soft tissue, in the body of a patient. The compositions include organic and inorganic matter. The compositions can be genetically produced or manipulated. The living organisms can be bacteria, viruses, or any other living organism which promote tissue growth. By way of example and not limitation, growth factors can include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (acidic/basis (FGF a,b), interleukins (IL's), tumor necrosis factor (TNF), transforming growth factor (TGF-B), colony-stimulating factor (CSF), osteopontin (Eta-1 OPN), platelet-derived growth factor (PDGF), interferon (INF), bone morphogenic protein 1 (BMP-1), and insulin growth factor (IGF). Recombinant and non-recombinant growth factors can be utilized as desired. Bacteria or viruses can, when appropriate, be utilized as growth factors. For example, there is a bacterial hydrophilic polypeptide that self-assembles into a nanometer internal diameter pore to build a selective lipid body. Various enzymes can be utilized for the synthesis of peptides which contain amino acids that control three-dimensional protein structure and growth. Growth factors can be applied in gels or other carriers which regulate the rate of release of the growth factors and help maintain the growth factors and the carrier, at a desired location in the body. Time release capsules, granules, or

other carriers containing growth factor can be activated by tissue pH, by enzymes, by ultrasound, by electricity, by heat, by selected *in vivo* chemicals or by any other selected means to release the growth factor. The carrier can be resorbable or non-resorbable. Or, the growth factor itself can be activated by similar means. Either the carrier or the growth factor can mimic extracellular fluid to control cell growth, migration, and function. The growth factor can be administered orally, systemically, in a carrier, by hypodermic needle, through the respiratory tract, or by any other desired method. The growth factor an also be administered into a capsule or other man-made composition or structure placed in the body. While administration of the growth factor is presently usually localized in the patient's body, circumstances may arise where it is advantageous to distribute a growth factor throughout the patient's body in uniform or non-uniform concentrations. An advantage to growth factors is that they can often, especially when in capsule form or in some other containment system, be inserted to a desired site in the body by simply making a small incision and inserting the growth factor. The making of such small incision comprises minor surgery which an often be accomplished on an out-patient basis. The growth factors can be multifactorial and nonspecific.

PAGE 44, LINE 19 – PAGE 46, LINE 16

Genetic material comprising a portion of a gene, a gene, genes, a gene product (i.e., a composition a gene causes to be produced like, for example, an organ-producing growth factor), growth factor, or an ECM (extracellular matrix) can be used in or on the body to grow an organ to tissue. For example, the vascular epithelial growth factor gene (VEGF) or its growth factor equivalent can be inserted into the body to cause an artery to grow. When insertion of a gene, portion of a gene, gene product, growth factor, or ECM *in vivo* or *ex vivo* is referred to herein in

connection with any of the implant techniques of the invention, it is understood that a cell nutrient culture(s), physiological nutrient culture(s), carrier (s), enhancer(s), promoter(s), or any other desired auxiliary component(s) can be inserted with the gene or at the same location as the gene, growth factor, ECM, etc.

An artery is an organ from the circulatory system. An artery can be grown in the heart, legs, or other areas by injecting a gene or other genetic material into muscle at a desired site. Size, vascularity, simplicity of access, ease of exploitation, and any other desired factors can be utilized in selecting a desired site. The gene is one of several known VEGF genes which cause the production of vascular endothelial growth factors. Several VEGF genes which produce vascular endothelial growth factors are believed to exist because nature intends for there to be several pathways (i.e., genes) which enable the production of necessary growth factors. The existence of several pathways is believed important because if one of the genes is damaged or inoperative, other similar genes can still orchestrate the production of necessary growth factors. VEGF genes are used by the body to promote blood vessel growth. VEGF genes are assimilated (taken in) by muscle cells. The genes cause the muscle cells to make a VEGF protein which promotes the growth of new arteries. VEGF proteins can be made in a lab and injected into a patient intravenously, intraluminally, or intramuscularly to promote the growth of an artery. Or, the genes (or other genetic material) can be applied with an angioplasty balloon, with the assistance of a vector, or by any other method.

It is not always desirable to grow a completely new organ. Sometimes growing a portion of an organ is desirable. For example, in some heart attacks or strokes, a portion of the heart or brain remains viable and a portion dies. An injection of a gene to form cardiac muscle and/or an injection of a gene to form an artery can be utilized to revive or replace the dead portion of the

heart. The dead portion of the heart may (or may not) be used as a matrix while the new muscles and vessels grow. Thus, in this example, a partial new organ is grown in a pre-existing organ. A pacemaker may (or may not) be necessary. A second injection of a gene may (or may not) be necessary to stop cardiac muscle growth once it is completed. Portions of organs throughout the body can similarly be repaired or replaced. It may be necessary to provide gene(s) or growth factor(s) sequentially. For instance, one or more blood vessels are grown by inserting an appropriate gene or other genetic material into a selected area. Second, an appropriate gene or other genetic material is inserted in the selected area to grow a bone or other organ.

The size and shape limitation of the desired structure can come from a containment and boundary contact inhibition phenomenon or by a chemical inhibition.

A variation on the theme of growing a portion of an organ is as follows: a portion of a heart dies. The pericardium is utilized as a scaffold and seeded with cells and/or genes to grow new muscle, and genes (or other genetic material) to grow new arteries. Immediately adjacent the dead cardiac muscle, onto or into the pericardium, the appropriate cells, genes, and/or growth factors (or other genetic material) are placed. Once the new muscle and blood vessels have grown, the function specific tissue can be applied to the damaged portion of the heart and paced, if necessary, to augment cardiac action. If the surgeon desires, the dead muscle can be removed and the new muscle and blood vessels can be surgically rotated into the excised region and secured. This probably can be done endoscopically. In essence, the pericardium is utilized to allow the new muscle wall to grow. The new muscle wall is then transplanted into the damaged heart wall. This procedure utilizes the body as a factor to grow an organ and/or tissue, after which the organ and/or tissue is transplanted to a desired region. On the other hand, the new muscle wall may integrate itself into the old wall and not require transplantation.

SECOND SUPPLEMENTAL DECLARATION
EXHIBIT B

CLAIMS
APPLICATION SERIAL NO. 09/836,750

236. A method of growing a new portion of a pre-existing heart comprising the steps of placing a growth factor in a body of a human patient and growing new cardiac muscle and growing a new artery in said heart.

238. The method of claim 236, further comprising repairing a dead portion of said heart.

239. The method of claim 236, further comprising repairing a damaged portion of said heart.

240. The method of claim 236, wherein said growth factor comprises genetic material selected from the group consisting of a portion of a gene, a gene, a gene product, and an extracellular matrix.

241. The method of claim 240, wherein said genetic material comprises a gene.

242. The method of claim 241, wherein said gene comprises VEGF.

243. The method of claim 236, wherein said growth factor comprises a member selected from the group consisting of cells, cellular products, and derivatives of cellular products.

244. The method of claim 243, wherein said growth factor comprises a cell

245. The method of claim 244, wherein said cell is multifactorial and non-specific.

246. The method of claim 245, wherein said cell comprises a stem cell.

247. The method of claim 236, wherein said growth factor is placed in said patient by injection.

248. The method of claim 247, wherein said injection is intravenous.

249. The method of claim 247, wherein said injection is intraluminal.

250. The method of claim 247, wherein said injection is intramuscular.

251. The method of claim 236, wherein said growth factor is placed in said patient by a carrier.

252. The method of claim 251, wherein said carrier comprises an angioplasty balloon.

253. The method of claim 236, wherein said growth factor comprises a gene and a cell.

254. A method of growing a new portion of a pre-existing organ comprising placing a growth factor in a body of a patient to grow new muscle in said organ.

255. The method of claim 254, wherein said organ comprises a heart.

256. The method of claim 255, wherein said new muscle comprises cardiac muscle and said growth factor comprises a stem cell.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: James P. Elia	)	
	)	
SERIAL NO.: 09/836,750	)	EXAMINER: E.C. Kemmerer, Ph.D.
	)	
FILED: April 17, 2001	)	
	)	GROUP ART UNIT: 1646
FOR: METHOD FOR GROWING MUSCLE IN A HUMAN HEART	)	

SECOND SUPPLEMENTAL DECLARATION
OF ANDREW E. LORINCZ, M.D.

I, Andrew E. Lorincz, declare as follows:

1. I reside at 13820 NW County Rd 235, Apt 8, Alachua, FL 32616-2098.

2. This Second Supplemental Declaration is submitted in addition to my previous Declaration dated June 5, 2003 and my Supplemental Declaration dated February 3, 2004. No changes are made to either of such previous Declarations.

3. My Curriculum Vitae (hereinafter "CV") is attached as Exhibit A to my previous Declaration.

4. It is my understanding that the Examiner in charge of the above-identified patent application, in an Office Action dated June 1, 2004 for related patent application Serial No. 09/794,456, questioned my qualification, for the first time, to render my previous opinions mentioned in above Paragraph 2. It is my further understanding that the basis for such questioning was that the Examiner noted that I did not report experience with cellular therapy. I desire to provide the

information contained in following paragraph 5 so that the Examiner can consider such information in this application, as well.

5. In addition to the qualifications set forth in my CV, I am familiar with stem cell technology, including bone marrow preparation.

6. I have read and understood the disclosures of the above-referenced patent application at page 20, line 10 through page 21, line 15; and page 44, line 19 through page 46, line 16. Such disclosures are the same as I read and understood in my previous Declaration and Supplemental Declaration. A copy of such disclosures is attached hereto as Second Supplement Declaration Exhibit A.

7. I note that the disclosures referenced in above Paragraph 6 relate to using a growth factor for promoting the growth of soft tissue and, more specifically, to a method which may use such growth factors for growing a new portion of a human heart by growing new cardiac muscle in the heart.

8. I have read and understood the claims set forth in Second Supplemental Declaration Exhibit B and have been informed that such claims are currently presented in this application.

9. Based upon above Paragraphs 6-8, it is my opinion that one skilled in the medical arts, armed with the knowledge in such paragraphs, would be enabled to practice the method set forth in Second Supplemental Declaration Exhibit B and to predictably anticipate the results defined therein without need for resorting to undue experimentation.

10. I believe that one skilled in the medical arts, upon reading the disclosures in above Paragraph 6, would understand that cellular growth factors, such as multifactorial and non-specific cells, are included in such disclosures. Moreover,

such skilled person would understand the disclosure on page 45 to be authored as an illustration of various modes of delivery of growth factors, whether they are genes or other genetic material; and that such skilled person would further understand that the disclosures on pages 45 and 46 describe genetic material to include appropriate cells and genes.

11. Declarant states that the above opinion was reached independently.

Declarant understands that (1) any willful false statements and the like made herein are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon, and (2) that all statements made of Declarant's own knowledge are true and that all statements made on information and belief are believed to be true.

Further Declarant sayeth not.

Date: 7-19-04

Andrew E. Lorincz, M.D.

Andrew E. Lorincz, M.D.

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APPLICATION SERIAL NO. 09/836,750

PAGE 20, LINE 10 – PAGE 21, LINE 15

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other carriers containing growth factor can be activated by tissue pH, by enzymes, by ultrasound, by electricity, by heat, by selected *in vivo* chemicals or by any other selected means to release the growth factor. The carrier can be resorbable or non-resorbable. Or, the growth factor itself can be activated by similar means. Either the carrier or the growth factor can mimic extracellular fluid to control cell growth, migration, and function. The growth factor can be administered orally, systemically, in a carrier, by hypodermic needle, through the respiratory tract, or by any other desired method. The growth factor an also be administered into a capsule or other man-made composition or structure placed in the body. While administration of the growth factor is presently usually localized in the patient's body, circumstances may arise where it is advantageous to distribute a growth factor throughout the patient's body in uniform or non-uniform concentrations. An advantage to growth factors is that they can often, especially when in capsule form or in some other containment system, be inserted to a desired site in the body by simply making a small incision and inserting the growth factor. The making of such small incision comprises minor surgery which an often be accomplished on an out-patient basis. The growth factors can be multifactorial and nonspecific.

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connection with any of the implant techniques of the invention, it is understood that a cell nutrient culture(s), physiological nutrient culture(s), carrier (s), enhancer(s), promoter(s), or any other desired auxiliary component(s) can be inserted with the gene or at the same location as the gene, growth factor, ECM, etc.

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heart. The dead portion of the heart may (or may not) be used as a matrix while the new muscles and vessels grow. Thus, in this example, a partial new organ is grown in a pre-existing organ. A pacemaker may (or may not) be necessary. A second injection of a gene may (or may not) be necessary to stop cardiac muscle growth once it is completed. Portions of organs throughout the body can similarly be repaired or replaced. It may be necessary to provide gene(s) or growth factor(s) sequentially. For instance, one or more blood vessels are grown by inserting an appropriate gene or other genetic material into a selected area. Second, an appropriate gene or other genetic material is inserted in the selected area to grow a bone or other organ.

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A variation on the theme of growing a portion of an organ is as follows: a portion of a heart dies. The pericardium is utilized as a scaffold and seeded with cells and/or genes to grow new muscle, and genes (or other genetic material) to grow new arteries. Immediately adjacent the dead cardiac muscle, onto or into the pericardium, the appropriate cells, genes, and/or growth factors (or other genetic material) are placed. Once the new muscle and blood vessels have grown, the function specific tissue can be applied to the damaged portion of the heart and paced, if necessary, to augment cardiac action. If the surgeon desires, the dead muscle can be removed and the new muscle and blood vessels can be surgically rotated into the excised region and secured. This probably can be done endoscopically. In essence, the pericardium is utilized to allow the new muscle wall to grow. The new muscle wall is then transplanted into the damaged heart wall. This procedure utilizes the body as a factor to grow an organ and/or tissue, after which the organ and/or tissue is transplanted to a desired region. On the other hand, the new muscle wall may integrate itself into the old wall and not require transplantation.

SECOND SUPPLEMENTAL DECLARATION
EXHIBIT B

CLAIMS
APPLICATION SERIAL NO. 09/836,750

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238. The method of claim 236, further comprising repairing a dead portion of said heart.

239. The method of claim 236, further comprising repairing a damaged portion of said heart.

240. The method of claim 236, wherein said growth factor comprises genetic material selected from the group consisting of a portion of a gene, a gene, a gene product, and an extracellular matrix.

241. The method of claim 240, wherein said genetic material comprises a gene.

242. The method of claim 241, wherein said gene comprises VEGF.

243. The method of claim 236, wherein said growth factor comprises a member selected from the group consisting of cells, cellular products, and derivatives of cellular products.

244. The method of claim 243, wherein said growth factor comprises a cell

245. The method of claim 244, wherein said cell is multifactorial and non-specific.

246. The method of claim 245, wherein said cell comprises a stem cell.

247. The method of claim 236, wherein said growth factor is placed in said patient by injection.

248. The method of claim 247, wherein said injection is intravenous.

249. The method of claim 247, wherein said injection is intraluminal.

250. The method of claim 247, wherein said injection is intramuscular.

251. The method of claim 236, wherein said growth factor is placed in said patient by a carrier.

252. The method of claim 251, wherein said carrier comprises an angioplasty balloon.

253. The method of claim 236, wherein said growth factor comprises a gene and a cell.

254. A method of growing a new portion of a pre-existing organ comprising placing a growth factor in a body of a patient to grow new muscle in said organ.

255. The method of claim 254, wherein said organ comprises a heart.

256. The method of claim 255, wherein said new muscle comprises cardiac muscle and said growth factor comprises a stem cell.